The intoxicated EEG

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Abstract: Highlights: * Here we report on accidental oxcarbazepine intoxication in a single patient. * In this patient we demonstrate EEG-documented acute downbeat nystagmus (DBN). * Such DBN most likely reflects acute oxcarbazepine-induced cerebellar-dysfunction. * New-onset DBN on EEG should prompt checking for antiepileptic drug-intoxication.

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THE INTOXICATED EEG

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Running title: Downbeat nystagmus on EEG

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Case description

A 38-year old male patient with pharmacoresistant bilateral temporal-lobe epilepsy was referred to our department for adjustment of antiepileptic-drug dosage with continuous Video-EEG monitoring.

In 2013, bilateral deep brain electrodes were implanted for chronic stimulation in both anterior thalamic nuclei. After implantation, the patient remained seizure free of generalized tonic-clonic seizures, but continued to experience daily complex-partial seizures typically presenting with initial dizziness, shortness of breath and a short period of unresponsiveness. Before admission, he was treated with levetiracetam (1g twice a day), lamotrigine (500mg twice a day) and oxcarbazepine (600mg twice a day). Due to insufficient seizure control and likely levetiracetam-associated aggressive behavior the following modifications were applied: At admission (day 1) levetiracetam dosage was reduced to the half (and completely stopped on day 3), while valproid acid was started at a low dose (300mg twice a day). Accidentally, on day 2 the oxcarbazepine dosage was doubled in the evening (from 600mg to 1200mg). The next day (day 3) the patient again received the double oxcarbazepine dose in the morning and few hours later he presented with acute vertigo, nausea and vomiting. Continuous EEG-monitoring showed steep surface-negative excursions followed by shallow return to baseline (frequency = 2-3/sec) that were most prominent in frontal derivations after eyes opening (Figure 1A, arrows). This pattern was interpreted as rhythmic eye movements with slow upward phase and fast downward phase, i.e., downbeat-nystagmus (DBN). On clinical neurological examination DBN was confirmed, while no other focal neurological deficits were found. Emergency brain CT was reportedly normal, excluding structural causes of acute DBN. Oxcarbazepine serum levels were supra-therapeutic (147.4µmol/l, therapeutic range = 11.8-138µmol/l; baseline serum level at admission: 72.8µmol/l), while serum levels of the other antiepileptic drugs either remained in the established therapeutic range (lamotrigine: 38.2µmol/l, therapeutic range=9.8-58.6) or did not reach therapeutic levels yet (valproid acid:

145µmol/l, therapeutic range=350-700). The increased DBN therefore most likely reflected acute oxcarbazepine-induced cerebellar dysfunction, resulting in impaired vertical gaze holding. Potentially, the simultaneous addition of valproid acid further increased oxcarbazepine serum levels as a result of its known enzyme inhibiting effect. The patient was transferred to intermediate care unit for monitoring and oxcarbazepine dosage was lowered again. Serum oxcarbazepine levels returned to the therapeutic range (41.3µmol/l) on day 5 and the patient's acute cerebellar signs and symptoms including DBN resolved completely. The reversibility of DBN was also demonstrated on re-established EEG-monitoring on day 5 (Figure 1B).

Posterior cerebellar lesions involving median/paramedian structures and especially the flocculus and the paraflocculus have been linked to DBN [1], typically demonstrating cerebellar atrophy in chronic cases. In patients with acute DBN, metabolic-toxic and structural causes such as lesions of the craniocervical junction including Arnold-Chiari malformation may cause cerebellar dysfunction. Neurotoxic effects of antiepileptic drugs resulting in DBN were frequently observed in patients with phenytoin [2] or carbamazepine overdosage [2, 3] and was shown to be reversible after adjustment of dose and subsequent reduction of drug blood levels. In the previous literature we identified however only a single patient with acute DBN caused by oxcarbazepine intoxication [4]. In contrast to carbamazepine, oxcarbazepine is not metabolized to an active toxic epoxide metabolite and intoxication symptoms are usually mild, which might explain why DBN in oxcarbazepine intoxication has rarely been reported.

Known as a sign of cerebellar loss of function [1], new-onset DBN on EEG and on clinical examination should prompt checking for structural lesions and drug toxicity in patients under antiepileptic drug-treatment. Prognosis of acute drug-induced DBN is usually excellent after adjustment of antiepileptic drug dosage and reduction of serum levels. This is in contrast to chronic DBN, which may be found in antiepileptic drug-induced cerebellar

degeneration (e.g., due to long-term phenytoin-intake) [5] and is usually persistent after cessation of the causing agent.

Figure 1:

EEG-recording in longitudinal bipolar montage (10/20 system). Panel A: At the time of oxcarbazepine intoxication (day 3), steep surface-negative excursions (arrows) are followed by more slow return to baseline. Considering eyeball polarity (positive to negative from ventral to caudal) this indicates *slow* upward eye-drift followed by *fast* downward saccades, consistent with DBN. Note that eye lid movements will contribute to these EEG changes as well [6]. Panel B: 48 hours later DBN had resolved, consistent with the return of oxcarbazepine blood levels to the therapeutic range.

Required statements

Author contributions to the manuscript

Dr. A. Tarnutzer: drafting of manuscript and analysis / interpretation of neurological findings and EEG recordings

Dr. L. Imbach: analysis and interpretation of EEG recordings, study supervision, critical revision of the manuscript for important intellectual content

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Disclosure of Conflicts of Interest:

None of the authors has any conflict of interest to disclose

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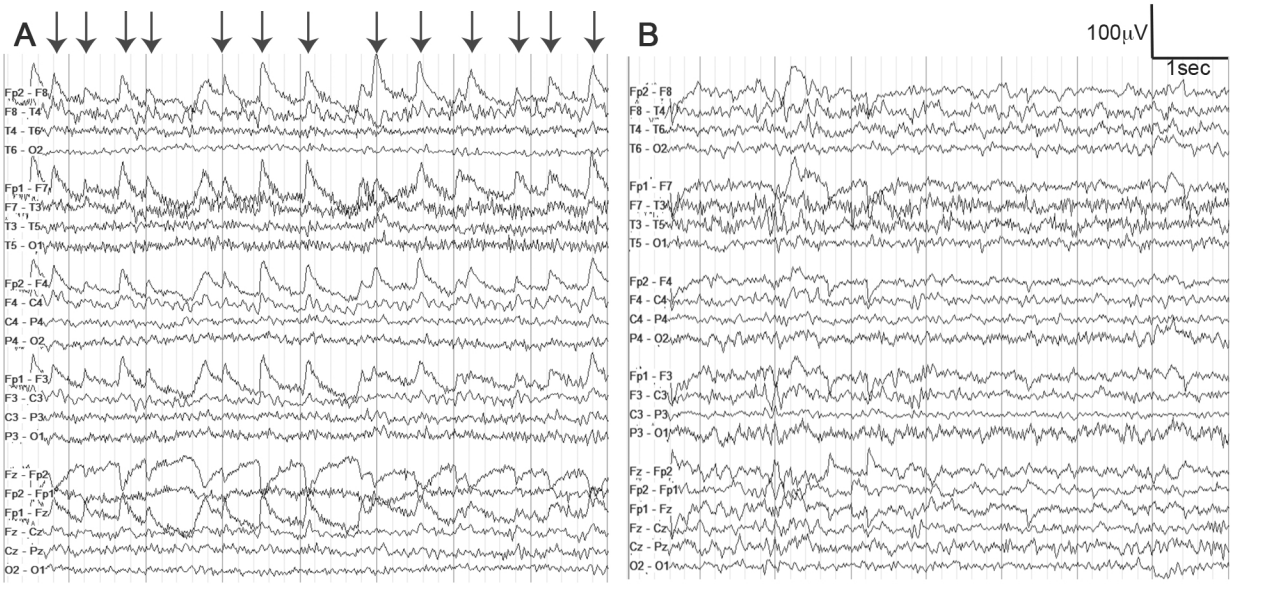
A
B
100μV
1sec
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Fp2
Fp2 - Fp1
Fp1 - Fz
Fz - Cz
Cz - Pz
O2 - O1